

reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained by the Examiner for reasons of record. Applicants respectfully traverse this rejection.

The Examiner comments that 4 species of cellulose derivatives is not adequate to describe the full breadth of cellulose derivatives as recited in claims 1 and 10.

The use of dietary fibers, as laxatives, is well known, and well documented in the art. Therefore, the skilled artisan would readily understand what is intended, and how to administer the dietary fibers in the novel use herein. The fibers themselves are not new, nor how they are administered. The present invention is directed to a novel use of particular fibers (water soluble, non-fermentable cellulose derivatives) in a particular method, i.e. the reduction of the incidence of colon and breast cancer. It should be noted that the law is well settled that Applicants are not required to provide working examples in order to meet the requirements of enablement. However, it should be noted that Applicants do provide such biological data in their specification.

While Applicants believe that the skilled artisan would readily understand what is meant by the term cellulose derivative within the context of water soluble, non-fermentable, Claims 1 and 10 have been amended. This amendment is solely to facilitate prosecution and not in acquiescence to the rejection.

Claims 1 to 3, 5 to 12 and 14 to 18 are also rejected under 35 USC §112, first paragraph as being nonenabling for the combination of fibers. Applicants respectively traverse this rejection.

Claims 1 and 10 (as amended) are directed to the use of water soluble, non-fermentable cellulose derivatives. The water soluble, non-fermentable cellulose derivatives may be taken by a patient with another fiber, such as an insoluble fiber (wheat bran), or a soluble fermentable fiber (psyllium), or a combination of all three types of fibers if they so choose. The claims all require that at least a water soluble, non-fermentable cellulose derivative be given.

The specification quite clearly teaches one how to determine each of these components, and provides a rational basis for such combination. As noted above, there is no requirement that the specification provide working examples. The choice of each class of fibers is readily identifiable, see specification and Applicants IDS/1449 form, such that a skilled artisan in this field would readily understand how to make and how to use the present invention.

The Examiner comments on page 4 of the office action that Claims 1 to 3, 5 to 12, and 14 to 18 are broadly drawn to method of administering combinations of fiber to mammals.... where the combinations may or may not include wheat bran. It is

believed that this is a rejection under 35 USC §112, first paragraph, but the record is unclear. Clarification is requested.

Applicants have found that water soluble, non-fermentable fibers have a use in a protective role against colon cancer and breast cancer. Protective effects have been previously been noted for insoluble fibers, and certain soluble fermentable fibers (see specification page 1, lines 34 to 37, and page 2, lines 1 to 6). It is the novel use of water soluble, NON-FERMENTABLE cellulose fibers that have now been found to reduce the incidence of these cancers.

This group of fibers may optionally be used in combination with any of the other types of fibers known in the art as cited herein. This is simply incorporating the prior art teachings with the novel discovery that water soluble non-fermentable fibers also have a protective effect. It is not seen how claims 1 and 10 are unclear in this matter. The specification provides data on the use of water soluble, non-fermentable cellulosic fibers (see examples 1 and 2). The specification also teaches how to administer these fibers with a second or third component, such as an insoluble fiber, such as wheat bran or a water soluble fiber if desired, see also Examples 1 and 2. The specification further provides data on how to formulate and administer said combinations, see page 7, lines 14 to 25. It should be noted that Applicants have incorporated by reference the disclosure of various cited references (over which Applicants are presently rejected) which teach how to administer both insoluble and water soluble fermentable fibers. Consequently it is not seen that the specification is unsupported in this aspect.

In view of these remarks and amendments, reconsideration and withdrawal of the rejection to the claims under 35 USC §112, first paragraph is respectfully requested.

#### **Rejection under 35 USC § 102(e)**

Claims 1, 2, 5, 6, 8, and 9 are rejected under 35 USC §102 (e) as being anticipated by Annison et al., US patent 5,840,860. Applicants respectfully traverse this rejection.

The Examiner maintains that "Annison's compound falls within the scope of the compounds used in the claimed methods". Annison et al. is directed to a method of delivering short chain fatty acids (SCFA's), i.e. butyrates, to the lower bowl which is bound to a carrier, preferably a carbohydrate (column 6, lines 45 –46). A wide range of carriers can be used. However, the carrier is perceived as being an active ingredient. The choice of a carrier include those listed on column 6, lines 54 to 67 and column 7, lines 1 to 64. In fact, Annison prefers a digestive starch as a carrier as

it can also be fermented by microorganisms in the colon to deliver additional SCFA's in addition to those linked to the carrier (see column 7, lines 12 to 17).

It should also be noted that there is a typographical error in column 7, line 3 in that microcrystalline has a comma after it. This leaves the term undefined. However, it is likely that this is a reference to microcrystalline cellulose ("cellulose" being the missing term).

The Examiner also comments that Annison teaches that the "method may be used for lowering the risk of a colon disorder... see claims 24-26, col. 24". Annison teaches in claim 24 that you can use an agent comprising a "carrier covalently bonded with a fatty acid by a bond that is hydrolysable in the colon to give a free fatty acid". That is clearly not the same method as claimed in claim 1 herein.

The present invention is distinguished in that the water soluble non-fermentable cellulose derivatives of the claims herein do not generate SCFA's. That is why the claim requires the use of a NON-FERMENTABLE fiber.

To better clarify this point, Applicants have amended claim 1 to water soluble non-fermentable fibers from the group listed on page 2, lines 17 to 20 in the specification, alone or with insoluble fibers. Therefore, the teachings of Annison et al. do not anticipate Applicants claimed invention herein.

In light of these remarks and amendments, Applicants respectfully request reconsideration and withdrawal of the rejection to the claims under 35 USC §102 (e).

#### **Rejection under 35 USC § 102(b)**

Claims 1, 2, 5, 6, 8, and 9 are rejected under 35 USC §102 (b) as being anticipated by Folino et al. (Folino, J. Nutr. 125: 1521-28, 1995). Applicants respectfully traverse this rejection.

Folino et al., teaches that epithelial proliferation, using a metaphase arrest method is dependent upon the type of fiber chosen for use, with methylcellulose > coarse wheat bran > fine wheat bran = rice bran > no fiber.

The end result of the teachings of the Folino et al. article is epithelial proliferation. The epithelial proliferation looked for is that of the rapidly dividing tissues or cells in the colon. This marker or result is not the same as looking for cancerous, or neoplastic cell differentiation. The Folino et al. method does not measure tumors, or tumor growth in contrast to that described herein.

Folino et al. concludes that methylcellulose will increase the rate of cell division, have a high stool output, it is acidic and will not ferment, therefore no SCFA's will be present, and there will be no decrease in the pH.

This result can be seen in the Abstract, wherein the effect on stool output is also described as ranking identically to that above. While this certainly confirms the use of methylcellulose as a laxative, it does not meet the preferred criteria of Folino et al. for the other desired aspects. The following sentence in the abstract discusses pH effects with most to least and methylcellulose is at the end, showing equal to a placebo or no fiber at all.

Folino et al. concludes that different fibers have different effects on the fecal environment, and are therefore hard to predict what the protective effect would be. Applicants are not claiming a general grouping of all types of dietary fibers, but a specific grouping of non-fermentable water soluble cellulose fibers. Applicants in contrast to Folino also demonstrate positive data on reducing the incidence of tumors (the claimed end result).

Folino et al. teaches that you can feed fibers to rats. It does not teach that these fibers are protective against colon cancer, alone or with wheat bran. It does not demonstrate a benefit, just that different conditions and variables could generate or give rise to differing risks.

The present invention looks at a measure of colon carcinogenesis, a precursor to tumors. The two examples herein clearly demonstrates that use of a water soluble, non-fermentable cellulose ether, such as Methylcellulose is effective to reduce the risk of colon cancer, using the aberrant crypt foci (see Example 1) method. This method is an art - recognized method for measuring cancerous and precancerous conditions in contrast to what is described in the Folino et al. article.

Folino et al. does not measure cancer, or even a precancerous condition. Folino et al. does not teach a method from which one can reach Applicants conclusion, nor does Folino et al. show a reduction of tumors. From the Folino et al. article you find 1 positive (or pro feature) for methylcellulose and 3 negative (or con features) described therein.

Therefore, Folino et al. does not anticipate Applicants claimed invention.

In light of these remarks and amendments, Applicants respectfully request reconsideration and withdrawal of the rejection to the claims under 35 USC §102 (b).

### **Rejection under 35 USC §103**

Claims 10, 11, 14, 15 17 and 18 are rejected under 35 USC §103(a) as being unpatentable over Annison et al. or Folino et al. , in view of Cohen et al. (J Nat'l Cancer Inst., 88(13): 899-907, 1996).

Claims 1, 4, 10 and 13 are rejected under 35 USC §103(a) as being unpatentable over Annison et al., or Folino et al, in view of Cohen et al. or Alabaster

et al. (Cancer Letters 75: 53-58, 1993). Applicants respectfully traverse all of these rejections.

As noted above, the present invention is directed to use of a water soluble, non-fermentable cellulose derivative, such as methylcellulose for the reduction of either colon cancer and/or breast cancer. It is not necessary to combine the methylcellulose with a second fiber, such as an insoluble fiber like wheat bran, or a soluble (but fermentable, fiber like psyllium).

Annison et al., is directed to an entirely different invention, which is delivery of a nutritional SCFA to the lower bowel. The SCFA's, such as butyrate, are a fermentable by-product from the water soluble, fermentable fibers. There is no teachings, or motivation, in the Annison et al. patent taken alone or in combination with any of the other references to direct the skilled artisan to utilize a methylcellulose for the reduction of the incidence of colon or breast cancer.

Prior to the cited Alabaster studies herein, it was shown that psyllium was not deemed protective against colon cancer. The first Alabaster et al. reference (Alabaster I – Cancer Letters 75:53-58, 1993) teach that wheat bran (and insoluble fiber) has a protective role, and that wheat bran in combination with psyllium is better than either alone. Alabaster II (Mutation Research 350:185-197, 1996), using the same type of experimental models, and the aberrant crypt foci method (as used by the present invention herein), also concludes that wheat bran alone, or in combination with psyllium and other nutrients, (see abstract) was effective to reduce aberrant crypt foci and colon tumors in their model.

Folino et al. shows that psyllium will decrease the pH, increase the level of butyrates (SCFA), increase output and as for proliferation, increase it over no fiber at all (placebo). Therefore, this article states that there are 3 positive measures for psyllium, and maybe one negative. Looking at this same article for methylcellulose, however, the skilled artisan is directed away from using methylcellulose over psyllium. Therefore, the skilled artisan would not be motivated to substitute an entirely different type of dietary fiber for psyllium.

Folino et al. also teaches, more importantly that the dietary fibers are not predictive, thereby teaching away from Applicants claimed invention. Folino et al. does not teach that use of methylcellulose would have a protective effect on carcinogenesis. Therefore, there is no motivation, taken alone or when combined with the other references which would direct the skilled artisan to the conclusion that methylcellulose would have a protective effect on colon cancer or breast cancer.

This deficiency is not solved by the Cohen et al. reference which is also a study on wheat bran and psyllium, but not water soluble non-fermentable cellulose

directives (as required by claims 1 and 10 herein). Similar to the Alabaster I and II studies, wheat bran is shown to be effective, and wheat bran in combination with psyllium is also effective to offer protection against breast cancer risk.

Cohen et al. does not teach nor suggest the use of water soluble non-fermentable cellulose derivatives. None of these references provide a basis to substitute or to include with wheat bran or psyllium a methylcellulose like product and expect to achieve Applicants claimed invention herein.

In light of these remarks and amendments, Applicants respectfully request reconsideration and withdrawal of the rejection to the claims under 35 USC §103 (a).

### CONCLUSION

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



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MARKED VERSION TO SHOW CHANGES

In the Specification:

The paragraph being at line 33, on page 7 has been amended as follows:

A suitable, alternative formulation for use herein includes, but is not limited to the fast dissolving methylcellulose tablets as described in Daggy et al., PCT/US98/17405, filed 8/21/98, now US Patent 6,350,469 or PCT/US98/17440, filed 8/21/98, now US Patent 6,372,253 whose disclosures are incorporated herein by reference in their entirety.

In the Claims:

Claims 3 and 12 have been cancelled.

The following claims have been amended:

1 (amended). A method of reducing the incidence of colorectal cancers in a mammal in need thereof, which method [comprises] consists essentially of administering to said mammal an effective amount of a water soluble, non-fermentable cellulose derivative selected from methylcellulose, ethylcellulose, carboxymethylcellulose and hydroxypropylmethylcellulose, alone or in combination with an insoluble fiber [and/or a soluble fermentable fiber].

2 (2x amended). The method according to Claim 1 wherein the water soluble, non-fermentable cellulose derivative is [a cellulose ether which is] methylcellulose, [ethylcellulose, carboxymethylcellulose,] or hydroxypropyl-methylcellulose [, or a combination thereof].

5 (2x amended). The method according to Claim 1 wherein the water soluble, non-fermentable cellulose derivative is methylcellulose [or hydroxypropyl-methylcellulose].

10 (amended). A method of reducing the incidence of breast cancer in a mammal in need thereof, which method [comprises ] consists essentially of administering to said mammal an effective amount of a water soluble, non-fermentable cellulose derivative selected from methylcellulose, ethylcellulose, carboxymethylcellulose and hydroxypropylmethylcellulose, alone or in combination with an insoluble fiber [and/or a soluble fermentable fiber].

12 (2x amended). The method according to Claim 10 wherein the water soluble, non-fermentable cellulose derivative is [a cellulose ether which is] methylcellulose, [ethylcellulose, carboxymethylcellulose,] or hydroxypropyl-methylcellulose [, or a combination thereof].

14 (2x amended). The method according to Claim 10 wherein the water soluble, non-fermentable cellulose derivative is methylcellulose [or hydroxypropyl-methylcellulose].